

Component-Resolved Diagnosis of Peanut Allergy and Its Possible Origins of Sensitization in China

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Key Words

Allergen component · Component-resolved diagnosis · Mugwort pollinosis · Nonspecific lipid transfer protein · Peach allergy · Peanut allergy

Abstract

Background: Clinical and immunological characteristics of food allergies vary depending on geographic regions. Little is known about peanut allergy in China. The aim of this study was to investigate the peanut sensitization profile in China. **Methods:** Thirty-eight participants with immunoglobulin E (IgE)-positive responses to peanuts (peanut-sensitized) were included in our study, and clinical characteristics were evaluated. Total and specific IgE reactivity against peanuts, other plant-derived foods, pollens, and related allergen components were determined. **Results:** Eighteen patients were symptomatic when exposed to peanuts. The majority of them presented with systemic reactions. More than half of the peanut-sensitized subjects also suffered from mugwort pollinosis and peach allergy. In patients with both peanut and peach allergies, reactions to peanuts were the same as or severer than those to peaches. Positivity rates of IgE response to rAra h 1–3, 8, and 9 in the peanut allergy group

were 5.6, 11.1, 5.6, 22.2, and 83.3%, respectively. 66.7% (12/18) of the peanut-allergic patients were monosensitized to rAra h 9. Anti-nArt v 3 [mugwort nonspecific lipid transfer protein (nsLTP)] IgE positivity in the peanut allergy group was significantly higher than that in the asymptomatic peanut-sensitized group. In Ara h 9 (peanut nsLTP)-sensitized patients with mugwort pollinosis, anti-nArt v 3 IgE levels were remarkably higher than anti-rAra h 9 (peanut nsLTP) IgE levels as well as anti-Pru p 3 (peach nsLTP) IgE levels. **Conclusions:** Ara h 9 was the major allergen of peanut, and Ara h 9 monosensitization was the most common peanut sensitization pattern in our population. Furthermore, there was a strong correlation between peanut sensitization and mugwort pollinosis, as well as peach allergy, in our country.

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Introduction

Peanut allergy is common in America and some European countries and often leads to life-threatening reactions [1–3]. Clinical and immunological characteristics of peanut allergy vary geographically. Patients from different areas of Europe show different peanut sensitization

patterns. In Spain for example, peanut-allergic patients are more often sensitized to the nonspecific lipid transfer protein (nsLTP) Ara h 9 in peanuts, and peanut allergy (PA) always follows other plant-derived food allergies, like peach [4, 5]. On the other hand, Swedish patients had relatively high IgE-positive responses to Ara h 8, a member of the PR-10 family and Bet v 1 homologue, which may be correlated with a high prevalence of birch pollinosis [6] and rarity of severe reactions. Ara h 1 and 2 are major peanut allergens in Austria, where anaphylaxis is the most common peanut-associated reaction [7]. In North America, most people were allergic to Ara h 1–3 (56.7–90.0%) and have a young onset age and severe symptoms [4].

Data from Singapore and the Philippines showed that local citizens had a lower prevalence of PA than those born in Western countries [8]. In Japan, Ebisawa et al. [9] found that measurement of Ara h 1-, 2-, and 3-specific immunoglobulin E (IgE) antibodies was useful for the diagnosis of peanut allergy in Japanese children and that rAra h 2 ImmunoCAP testing was able to differentiate between peanut-allergic and asymptomatic peanut-sensitized children, similar to studies from Western countries [10–12]. Component-resolved diagnosis of PA in Taiwan also showed that Ara h 1–3 were the major peanut allergens in local patients, and peanut-allergic children had persistent elevation of Ara h 2-specific IgE [13]. In Thailand, Ara h 2 is a unique and major peanut allergen, and the ratio of Ara h 2 to peanut-specific IgE (sIgE) was found to be useful in predicting severe reactions [14]. Little is known about the situation of PA in mainland China today. Herein, we investigated peanut sensitization profiles of mainland Chinese subjects and examined the potential relationship between PA and the local prevalence of pollinosis and peach allergy.

Methods

Subjects

A total of 38 peanut-sensitized participants were recruited in the current study. Eighteen were symptomatic upon peanut exposure and included in the PA group; 3 of them presented with only isolated oropharyngeal symptoms (oral allergy syndrome), and the remaining 15 developed one or more of the following: generalized urticaria, allergic rhinitis, asthma, gastrointestinal symptoms, or hypotension with or without oral reactions. Twenty patients sensitized but tolerant (asymptomatic) to peanuts were included in the peanut tolerance (PT) group. All participants were recruited as outpatients from the Allergy Department at Peking Union Medical College Hospital (Beijing, China) from April 2011 to January 2012. Food allergies were diagnosed on the basis of a compelling history,

and confirmed IgE sensitization. Pollinosis was defined as seasonal rhinitis and/or asthma occurring only in the corresponding pollen season, together with a confirmed positive IgE response to a pollen extract. Our research protocol was approved by the Ethical Committee of Peking Union Medical College. Written informed consent was obtained from each participant prior to study inclusion.

Serological Analysis

Total IgE and sIgEs against peanuts, peanut components (rAra h 1–3, 8, and 9), peach, peach nsLTP (rPru p 3), mugwort, and mugwort nsLTP (nArt v 3) were detected by the ImmunoCAP system (Thermo Fisher, Uppsala, Sweden). We used 0.35 kU/l as a cutoff for sIgEs against whole extracts of peanut, peach, and pollens, while 0.1 kU/l was used as a cutoff for IgE antibodies against peanut components according to a previous study [15]. Clinical characteristics and IgE antibody titers were analyzed and compared between different subgroups.

Statistical Analysis

SPSS 16.0 statistical software (SPSS Inc., Chicago, Ill., USA) was used to analyze the data. Frequencies of qualitative variables were compared by Pearson's χ^2 test or Fisher's exact test. Spearman's rank coefficient (ρ) was used to quantify correlations between variables. Comparison of quantitative variables was carried out using the Student's *t* test in case of normally distributed data or the Mann-Whitney *U* test in case of nonnormal distribution. A *p* value <0.05 was considered statistically significant. Bonferroni's correction was used when multiple comparisons were performed.

Results

Clinical characteristics of the 18 PA and 20 PT participants are shown in table 1. Total IgE levels of PA patients were significantly lower than those of PT subjects (medians: 113.6 vs. 480.0 kU/l, respectively, *p* = 0.001). In addition, the ratio of peanut-specific to total IgE in PA patients was significantly higher than that in the PT group (medians: 0.0237 vs. 0.0063, respectively, *p* = 0.009). More than half of the 38 total peanut-sensitized subjects also suffered from allergies to pollen and other plant-derived foods. The most prevalent pollen allergy was to mugwort (PA: 55.6%; PT: 70.0%), and the most frequent plant food allergies were to peaches (PA: 72.2%; PT: 55.5%) and then apples (PA: 33.3%; PT: 35.0%). The total prevalence of other plant food allergies was higher in PA than in PT patients (94.4 vs. 65%, respectively, *p* = 0.026). Five and 4 patients were respectively allergic to walnuts and hazelnuts in the PA group, but none in the PT group (table 1).

Clinical reactions to peanuts and peaches are shown in table 2. Generalized urticaria with or without angioedema of the skin (9/18) was the most common symp-

Table 1. Clinical characteristics of subjects in the PA and PT groups

Characteristics	PA group (n = 18)	PT group (n = 20)
Mean age $\pm$ SD, years	29.7 $\pm$ 14.2	22.6 $\pm$ 10.7
Males, n	10 (55.6)	9 (45.5)
Median IgE, kU/l		
tIgE	113.6 [19.9–2,462.0]	480.0 [128.2–2,642.5]
psIgE	2.64 [0.36–16.2]	3.80 [0.4–16.9]
psIgE/tIgE	0.0237	0.0063
Other plant food allergies, n	17 (94.4)	13 (65.0)
Peach	13 (72.2)	11 (55.5)
Apple	6	7
Melon	0	4
Kiwi	1	0
Walnut	5	0
Hazelnut	4	0
Sesame	1	0
Soybean	4	0
Potato	0	1
Tomato	0	1
Garlic	2	0
Pollen allergies, n	11 (61.1)	17 (73.7)
Birch	3 (16.7)	8 (40.0)
Mugwort	10 (55.6)	14 (70.0)

Figures in parentheses indicate percentages, those in square brackets are ranges. SD = Standard deviation; psIgE = peanut-specific immunoglobulin E; tIgE = total immunoglobulin E.

tom, followed by oral allergy syndrome (8/18) and gastrointestinal reactions (5/18). In the PA group, 13 patients were also allergic to peaches. All of them presented with the same clinical reactions to peaches and peanuts, except 2 who had severer reactions to peanuts than to peaches (table 2). In the PT group, 11 patients suffered from peach allergy, and the most frequently involved organ/tissue was the oral cavity (50%), followed by the skin (25%). IgE results of all the 38 subjects are presented in the online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000446156). Fifteen of the PA patients were sensitized to rAra h 9, among whom 12 were monosensitized. Positivity rates of the IgE response to allergen components are shown in figure 1. Anti-nArt v 3 IgE positivity was higher in the PA group than in the PT group (88.9 vs. 55.0%, respectively, $p = 0.021$). Among the 38 peanut-sensitized subjects, 24 (10 PA; 14 PT) also suffered from mugwort pollinosis. Of these 24 patients, anti-rAra h 9 (peanut LTP) IgE levels were significantly correlated with anti-nArt v 3 (mugwort LTP) IgE levels ($\rho = 0.629$; $p = 0.001$). Additionally, 24 (63.2%) of the 38 peanut-sensitized subjects were also allergic to peaches. Anti-rAra h 9 IgE values were closely

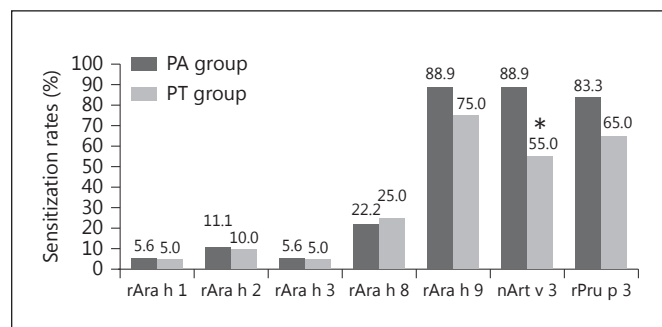


Fig. 1. Percentage of IgE-positive responses to allergen components in the PA and PT groups. * $p = 0.021$.

related to anti-rPru p 3 (peach LTP) IgE values ($\rho = 0.934$; $p < 0.001$).

A total of 29 subjects were sensitized to rAra h 9 (using 0.10 kU/l as a cutoff). According to the presence or absence of peanut- as well as mugwort-associated allergic reactions, these Ara h 9-sensitized subjects were further divided into 4 subgroups (groups A–D,) as shown in figure 2a. In Ara h 9-sensitized subjects with mugwort pollinosis,

Table 2. Clinical reactions to peanuts and peaches in both the PA and PT groups

	Affected organs/systems									
	oral cavity		skin		gastrointestinal tract		respiratory system		cardiovascular system	
	peanut	peach	peanut	peach	peanut	peach	peanut	peach	peanut	peach
<i>PA group</i>										
1				+	+				+	
2					+	+				
3	+	+								
4					+	+				
5							+	+		
6			+	+						
7	+	+	+	+						
8	+		+							
9			+	+						
10			+	+					+	
11			+						+	
12	+		+							
13							+			
14	+		+							
15			+	+	+	+	+	+		
16	+	+								
17	+	+								
18	+	+			+	+	+	+		
<i>PT group</i>										
1		+								
2										
3		+		+						
4										
5										
6										
7		+				+				
8										
9		+								
10		+								
11										
12										
13										
14		+		+						
15		+		+						
16										
17		+								
18		+								
19				+						
20		+		+						

IgE levels of anti-Ara h 3 were remarkably higher than those of anti-Ara h 9 (group A median: 18.29 vs. 0.86 kU/l, respectively, $p = 0.013$; group C median: 42.73 vs. 5.73 kU/l, respectively, $p < 0.01$), as well as anti-Pru p 3 (group A median: 18.29 vs. 4.53 kU/l, respectively, $p = 0.016$; group C median: 42.73 vs. 7.28 kU/l, respectively, $p < 0.01$).

After Bonferroni's correction, the differences mentioned above were still statistically significant. Furthermore, Ara h 9-allergic patients without mugwort pollinosis (group B) tended to have higher IgE levels of anti-Pru p 3 (median: 31.47 kU/l) than that of anti-Ara h 3 (median: 5.56 kU/l) as well as anti-Ara h 9 (median: 18.90 kU/l) (fig. 2b).

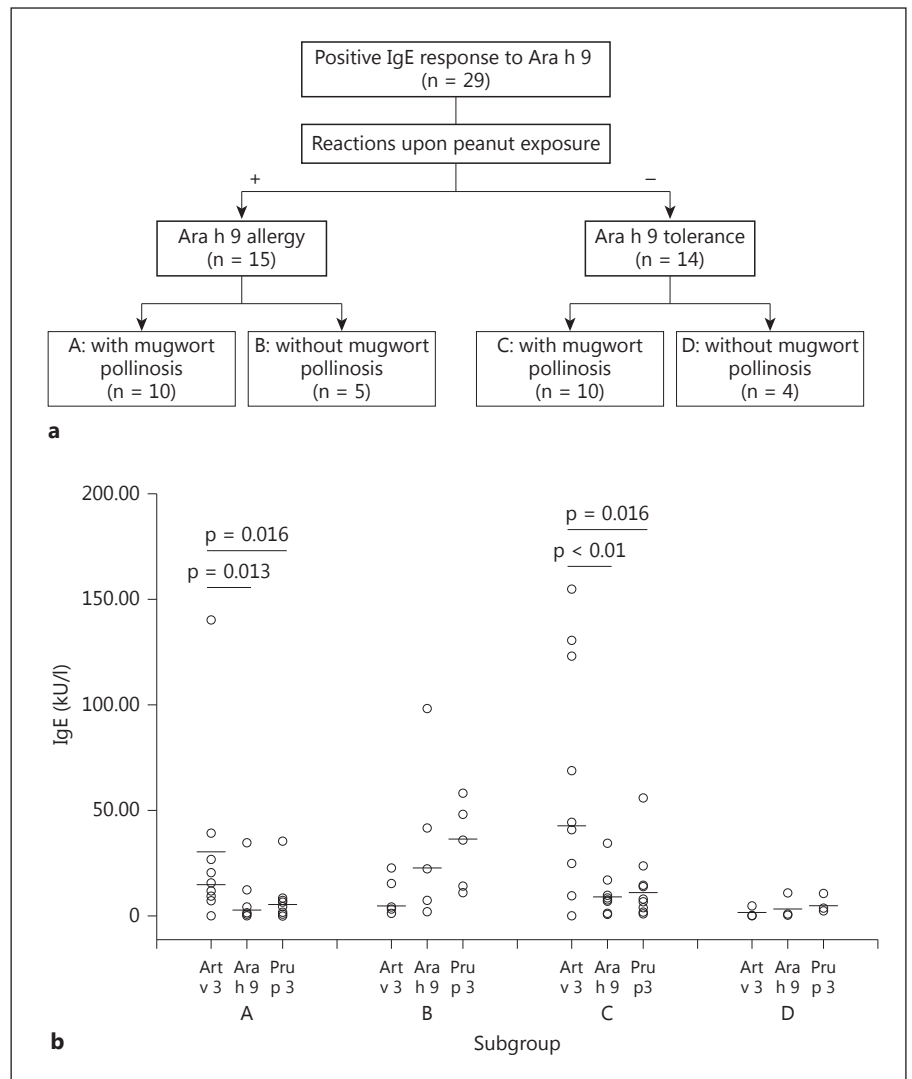


Fig. 2. a Subgroups A–D of Ara h 9-sensitized subjects. **b** Art v 3-, Ara h 9-, and Pru p 3-specific IgE levels in different subgroups of the 29 Ara h 9-sensitized patients.

Discussion

PA is a worldwide health problem and faces many challenges [16]. Previously reported clinical characteristics and sensitization patterns of PA worldwide had distinctive geographical differences. In comparison to America and other Western countries, PA is far less prevalent in China, despite the large amounts of peanut consumption in China [17]. Beyer et al. [18] investigated the effects of cooking methods on peanut allergenicity and concluded that the methods of frying or boiling, as practiced in China, appeared to reduce the allergenicity of peanuts comparing to the method of dry roasting practiced widely in the USA. Kopper et al. [19] also found that roasting decreased the solubility and increased the aller-

genicity of peanut proteins. In addition, Vissers et al. [20] found that extensive heating like roasting significantly increased the degranulation capacity of Ara h 1. These findings are quite helpful in understanding the relatively low prevalence of PA in China. However, the real sensitization profile and origin of PA in our population remain unclear. Thus, our study was performed to answer this question.

In this study, we analyzed the sensitization patterns of 38 subjects with a positive IgE response to peanut extract. Eighteen of them were symptomatic upon peanut exposure, and the others could tolerate peanuts well. Ara h 9 was the major allergen of peanuts, and monosensitization to Ara h 9 was the most common peanut sensitization pattern in China (fig. 1). These results were in line with

the findings from South Europe [4]. Like peach major allergen Pru p 3 of our population, Ara h 9 was also a member of the nsLTP family. nsLTPs are substantially stable and not degraded by heat or digestive enzymes [21–23]. Thus, boiled or fried peanuts as cooked in China could still elicit reactions in patients allergic to Ara h 9. Ara h 9-allergic reactions might differ in different populations. Moverare et al. [24] found that Ara h 9 sensitization was not associated with severe symptoms in Swedish patients, whereas 4 of the 5 patients presenting with severe reactions involving multiple systems in our study were mono-sensitized to Ara h 9. The only person who had a peanut-specific IgE level higher than 15 kU/l and manifested severe symptoms involving multiple systems was sensitized to neither of the 5 peanut components tested in our study. Some other clinically relevant peanut allergen component, such as Ara h 6, may exist in our population. Asaranoj et al. [25] had reported a case of anaphylaxis to peanuts in a patient with a high level of anti-Ara h 6 IgE but a low level of anti-Ara h 2 IgE. Further studies should take this allergen into consideration.

Scala et al. [26] investigated the prevalence of nsLTP sensitization in a large Italian cohort and found that there was a correlation between sensitization to pollen and plant food nsLTPs, and mugwort pollen extracts could inhibit 50–100% IgE binding to food nsLTPs. All the subjects included in this study were from northern China, where mugwort produces the most common allergenic pollens that lead to seasonal rhinitis and/or asthma in late summer and autumn [27]. Previous studies had shown that mugwort nsLTP Art v 3 was a promoter of peach sensitization in China [28, 29]. In this study, in total 63.2% (24/38) of the peanut-sensitized patients also suffered from mugwort pollinosis. IgE values of anti-nArt v 3 were significantly correlated with that of anti-rAra h 9 in peanut-sensitized patients with mugwort pollinosis. In addition, positivity of the IgE response to nArt v 3 in the PA group was remarkably higher than that in the PT group. In Ara h 9-sensitized patients with mugwort pollinosis, serum values of anti-nArt v 3 IgE antibodies were remarkably higher than those of anti-rAra h 9 IgE antibodies as well as anti-Pru p 3 IgE antibodies (fig. 2b). Using an ImmunoCAP inhibition method, Gao et al. [29] showed that mugwort Art v 3 played a dominant role in peach sensitization as a primary sensitizer. It was a pity that we did not perform the immunoCAP inhibition test to further confirm the relationship between Ara h 9 and Art v 3 sensitization, due to the lack of patient sera and purified or recombinant allergen components. However, considering PA has a similar sensitization profile to peach allergy and

a close relationship with mugwort pollinosis, mugwort pollen may also be a strong promoting factor for peanut sensitization, as it is for peach in China [28, 29].

During the last few decades, IgE cross-reactivity between LTPs from Rosaceae and from botanically unrelated plant foods has been profoundly researched [30, 31]. Interestingly, peach always seems to be the primary sensitizer [5, 32], and cross-reactivity to nsLTPs from botanically unrelated vegetables or seeds seems to depend on the level of Pru p 3 (peach nsLTP)-specific IgE [32]. In contrast to the less prevalent peanut allergy, peach allergy is very common in China, even the most common in patients with birch and/or mugwort pollinosis (data not published). In this study, all the 38 peanut-sensitized patients showed a positive IgE response to peach, among whom 63.2% had allergic reactions upon peach exposure. Peach nsLTP (rPru p 3) and peanut nsLTP (rAra h 9) had a strong IgE cross-reactivity to each other [33]. A high correlation between sensitization to rPru p 3 and rAra h 9 was also found in this study. Fourteen peanut-sensitized patients were free of mugwort pollinosis (8 in the PA group, 6 in the PT group), among whom 10 were allergic to peach. As high as 87.5% (7/8) of the PA patients without mugwort pollinosis were found to be suffering from peach allergy. In addition, anti-Pru p 3 IgE values seemed to be higher than anti-Ara h 9 IgE values in Ara h 9-sensitized patients without mugwort pollinosis, although this is statistically not significant in case of a small sample. Taken together, peach might be another origin of peanut sensitization in our population as it did in the Mediterranean area [5].

Interestingly, lower total IgE levels and a higher ratio of peanut-specific to total IgE were found in PA patients, compared to PT subjects (table 1). This was in accordance with a study by Mehl et al. [34] which showed that a higher ratio of sIgE to total IgE correlates with an increased probability of symptomatic food allergy. A higher level of total IgE seemed to be a protective factor against the translation from peanut sensitization to symptomatic PA. It is well known that IgE antibodies recognize and bind with specific epitopes comprised of several amino acids from an allergen molecule. IgE antibodies generated against the same allergen with multiple epitopes are polyclonal in nature and bind their respective epitopes with different affinities [35, 36]. Allergens capable of eliciting an allergic reaction have at least 2 epitopes. IgE-associated symptoms were triggered following the coupling of the IgE receptors on the surface of the effector cells binding the same type of sIgE; more irrelevant IgEs on the surface of the same effector cell in case of a higher level of total

IgE antibodies may interfere in the coupling of the corresponding IgE receptors.

PA patients could also be allergic to tree nuts. Walnut and hazelnut were the most common allergenic tree nuts in this cohort of PA patients. It is known that walnut and peanut co-allergy, as well as hazelnut and peanut co-allergy, is associated with cross-reactive T-cell responses [37, 38], other than cross-reactive IgEs [39].

Although placebo-controlled, double-blind food challenge is the gold standard for the diagnosis of food allergies, it is not routinely used in daily practice in our country where the medical environment is tough and violence acts against doctors and nurses are not occasional events. The potential risk of severe reactions during the challenge may provoke big trouble for the clinicians who perform it. However, all patients included in the present study had a convincing history of allergy and confirmed IgE sensitization tested by reliable ImmunoCAP technology. In both the PA and PT groups, peanut sensitization patterns were quite similar. Therefore, the findings of this study were convincing.

In summary, Ara h 9 was the major peanut allergen, with Ara h 9 monosensitization being the most common peanut sensitization pattern in our country. Moreover, prevalence of mugwort pollinosis may be a strong promoting factor for peanut, as well as peach, sensitization [18]. Consequently, peaches might be another origin of peanut sensitization in patients without mugwort pollinosis.

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Disclosure Statement

The authors have nothing to disclose.

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Peanut allergy. No.	Specific IgEs									
	peanut	Ara h					mugwort	Art v 3	peach	Pru p 3
		1	2	3	8	9				
1	8.03	0.03	0.05	0.03	0.05	75.23	5.25	4.32	33.82	53.38
2	0.62	0.00	0.01	0.00	1.42	0.06	0.03	0.00	3.26	0.53
3	0.98	0.03	0.03	0.02	3.60	1.11	11.93	16.12	7.32	1.27
4	13.50	0.00	0.00	0.00	0.00	18.90	12.40	16.50	47.00	43.50
5	8.10	0.14	0.18	0.14	0.13	3.44	128.46	140.26	29.90	9.19
6	0.86	0.00	0.00	0.00	0.00	1.71	47.53	39.32	6.55	6.96
7	11.19	0.00	0.01	0.00	0.00	33.24	13.12	23.94	29.29	31.47
8	2.70	0.00	0.00	0.00	0.00	0.12	22.17	26.76	9.39	0.04
9	1.27	0.00	0.01	0.00	0.00	25.75	11.25	20.81	33.32	35.52
10	2.58	0.01	0.00	0.00	0.00	7.76	2.86	5.56	9.65	10.01
11	0.97	0.00	0.00	0.00	0.00	0.49	8.91	12.15	3.18	3.80
12	3.38	0.01	0.01	0.00	0.00	9.24	3.86	7.48	5.64	7.73
13	4.41	0.06	0.63	0.07	0.11	0.15	0.40	0.06	0.75	0.55
14	0.68	0.01	0.03	0.01	0.01	3.82	1.79	2.11	5.69	6.78
15	16.22	0.00	0.02	0.00	0.00	0.05	85.50	109.34	38.41	0.18
16	6.46	0.00	0.01	0.00	0.00	0.33	20.26	20.46	10.65	1.89
17	1.81	0.06	0.06	0.02	0.03	0.10	1.72	0.36	1.77	0.28
18	0.36	0.00	0.00	0.00	0.00	0.60	8.37	9.46	4.10	5.25
Peanut tolerance No.										
1	9.59	0.01	0.01	0.00	0.00	0.01	38.64	0.02	19.76	0.20
2	2.41	0.03	0.02	0.02	0.01	4.86	76.00	0.19	3.48	4.04
3	8.92	0.05	0.05	0.04	0.04	6.07	109.98	122.98	64.78	55.27
4	0.70	0.01	0.01	0.00	0.01	0.03	36.87	13.55	6.02	0.04
5	16.88	0.41	0.42	0.19	0.29	0.28	11.81	0.21	11.49	0.17
6	7.12	0.05	0.05	0.03	7.67	7.53	33.32	44.50	32.97	8.16
7	0.97	0.01	0.01	0.00	30.28	0.01	0.23	0.00	14.26	0.00
8	0.81	0.07	0.11	0.09	0.20	0.15	74.73	0.30	1.17	1.58
9	2.26	0.07	0.02	0.01	81.79	0.74	0.05	0.00	43.84	1.88
10	0.99	0.01	0.03	0.02	0.02	0.34	21.63	25.06	2.01	0.59
11	6.94	0.02	0.04	0.02	0.01	0.03	21.79	0.02	14.86	0.09
12	4.10	0.01	0.02	0.01	0.03	8.06	3.03	4.81	8.30	8.39
13	7.43	0.03	0.04	0.03	0.02	0.05	20.78	0.03	21.78	0.22
14	10.33	0.01	0.03	0.01	5.99	12.58	111.68	130.31	18.82	13.41
15	3.52	0.01	0.01	0.00	0.00	5.40	29.98	40.98	5.98	6.40
16	2.06	0.02	0.00	0.00	0.00	0.86	18.32	9.64	6.42	1.46
17	6.05	0.00	0.02	0.01	0.01	25.52	121.46	154.63	18.88	14.28
18	1.09	0.00	0.02	0.01	0.01	0.87	71.19	68.80	3.69	0.73
19	7.00	0.01	0.01	0.00	0.00	7.21	44.94	40.73	34.20	23.22
20	0.40	0.00	0.00	0.00	14.57	0.01	0.05	0.00	1.76	0.00